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The Effect of Age, Sex and Pathologic Type on Risk of Multiple Polyps in a Chinese Teaching Hospital Based Study

Title Page

The Effect of Age, Sex and Pathologic Type on Risk of Multiple Polyps in a Chinese Teaching Hospital Based Study

Running title: risk factors for multiple polyps

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/1751-2980.12863

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Competing Interests

The authors declare that they have no competing interests.

Running title: risk factors for multiple polyps

Abstract

Aim: The lack of risk profile data regarding changes in multiple polyps identified by colonoscopy constrains the creation of evidence-based guidelines. This retrospective case-control study addresses this issue by characterizing the relationship between size, location and histology of multiple polyps, in addition to population-associated features in a large teaching hospital-based Chinese population.

Methods: A large, case-control retrospective analysis was conducted on polyps obtained from 8308 patients who presented at the Digestive Endoscopy Center, Changhai Hospital, Shanghai, China from January 2013 to August 2015. A total of 10572 polyps were analyzed, with risk factors extrapolated through chart review of patient electronic medical records.

Results: Single polyps were identified in 6843 patients (82.4%) while multiple polyps were found in 1465 (17.6%). Multivariate analysis indicated that males were more likely to have multiple polyps ($p<0.001$).

Compared with patients with single polyps, the numbers of those with multiple polyps increased significantly as age increased ($p<0.001$). Small (6-9mm) non-advanced adenomas were more likely to be found as multiple adenomas than were diminutive (<5mm) non-advanced adenomas ($p<0.000$). While the majority of the advanced and non-advanced adenomas were diagnosed in patients with single adenomas (56.0% and 65.4%, respectively), the advanced adenomas were more likely to be in multiples compared with non-advanced adenomas ($p<0.001$).

Conclusions: Our data indicate that particular features of colorectal polyps such as their large size, advanced histology and patient demographics including gender and age are risk factors associated with multiple polyps during diagnosis, screening and surveillance.

Keywords: Colon polyp, risk factors, multiplicity

Introduction

Colorectal cancer (CRC) is a common and lethal disease. In China, the incidence of colorectal cancer has continued to increase since 1998. It is

currently the sixth most common form of cancer and the fifth leading cause of cancer-related death in the country, contributing to an estimated 149772 deaths in 2011.[1] CRC is therefore an important public health concern in China due to its rising incidence and prevalence, in addition to the burden of disease.

There is robust evidence indicating that early detection by screening and removal of cancer precursor lesions offers an effective method of reducing colorectal cancer morbidity and mortality.[2] However, clinically, the majority of polyps do not cause symptoms. A key method of determining the suitability of cancer surveillance is risk stratification of the findings during colonoscopy screening and applying updated guidelines for colorectal cancer surveillance.

Due to the limitations of studies using prospective data, detailed subdivision in follow-up surveillance is lacking for patients with multiple polyps in Asian countries such as China. Asia Pacific consensus recommendations on colorectal cancer screening were adapted from the US Multi-Society Task Force (USMSTF) on colorectal cancer guidelines for colonoscopy surveillance. However, the USMSTF guidelines do not apply worldwide due to different population characteristics in Europe,

America and Asia. For example, two different strategies are used in follow-up surveillance for patients with more than one polyp in US and United Kingdom risk-stratification guidelines.[3,4,5] A single examination after one year is recommended in the U.K for patients with more than 5 small adenomas or more than 3 if at least one is ⩾1cm. In contrast, the U.S. guidelines recommend a shorter interval for those with more than 10 adenomas.

The primary aim of this study was to identify high risk features of multiple polyps based on size, location and histological type. Patient age and gender were also characterized on the basis of a contingency analysis of a large series of Chinese patients with colorectal polyps. These data provide important information on risk factors associated with multiple polyps, which will serve as evidence for an individualized approach to colonoscopy screening guidelines in China.

Methods

Study Population and Data Sources

This study was designed as a case control retrospective analysis of biopsies obtained from patients undergoing screening colonoscopy at the

Digestive Endoscopy Center, Changhai Hospital between January 2013 and August 2015. The procedures were performed by eight fully-trained, experienced gastroenterologists.

All biopsies and resected polyps were submitted to the Department of Pathology, Changhai Hospital for review. Exclusion criteria included: patients with hereditary CRC syndromes, such as Lynch syndrome, familiar adenomatous polyposis and Peutz-Jeghers syndrome; a history of inflammatory bowel disease; missing pathology report from index colonoscopy, or incomplete colonoscopic assessment as a result of inadequate bowel cleansing or lack of caecum intubation. A total of 8308 patients were included in the study, representing a total of 10572 biopsied polyps. This study was approved by the Shanghai Changhai Hospital Ethics Committee. All procedures conformed to the Declaration of Helsinki. Written, informed consent was obtained from all participants.

Measures and Definitions

Patient demographics (age and gender), polyp characteristics (size,

multiplicity, location and pathologic diagnosis) were collected from a review and analysis of electronic medical records. At the time of submission, gross descriptions of the biopsies were recorded in the database. All biopsies were fixed in formalin and systematically processed.

Colorectal polyps were histologically classified as either non-neoplastic, colorectal adenomas or serrated lesions by reference to a standardized set of diagnostic terms used by pathologists.[6] Non-neoplastic polyps were classified as inflammatory, lymphoid or juvenile. Juvenile polyps of the colon are of benign and hamartomatous and are the most frequent gastrointestinal polyp observed in children.[7, 8] Juvenile polyps have a cystic appearance with spaces filled with mucous and prominent irregular cystically dilated glands with lymphoplasmacytic infiltration. Lymphoid polyps consist of well differentiated lymphoid tissue, characterized by small, uniformly localized or generalized polypoid lesions. Colorectal adenomas encompassed tubular, tubulovilla, villous adenomas. Meanwhile, colorectal adenomas are classified as either non-advanced adenomas or advanced adenomas based on their pathologic characteristics.[9] Advanced adenomas are defined as either $\geqslant$10mm in

diameter, polyps with high grade dysplasia, tubulovillous adenoma containing >25% villous architecture or villous adenoma.[11,12] The definition of advanced histology of adenomas is that polyps with severe dysplasia and/or villous component, features predicting an increased likelihood of malignant transformation. Serrated lesions are identified by reference to the WHO classification,[10] being are slightly elevated lesions with irregular borders and possibly covered with mucus, as observed endoscopically.[13] Serrated adenomas are typically distorted with widened, 'boot-shaped' crypt bases.[14] Polyps are categorized by size into three groups: diminutive (⩽5mm), small (6–9mm) or large (⩾10mm). The location of polyps are defined as proximal if located in the cecum, ascending colon or transverse colon, or distal for all polyps found from the descending colon to the rectum. In the present study, we have defined multiple adenomas or polyps as the presence of 2 or more adenomas or polyps.

Analytical approach

Pearson chi-square analysis and Cochran-Mantel-Haenszel general association statistic were conducted using SPSS for bidirectionally unordered contingency tables. Wilcoxon rank-sum and

Cochrane-Mantel-Haenszel tests of row mean score differences for single ordinal contingency data were performed. A Spearman rank correlation analysis was performed and Cochrane-Mentel-Haenszel correlation statistic calculated for bidirectionally ordinal contingency tables. Results are reported as odds ratios (ORs) with 95% confidence intervals (CIs) and P-values. For all comparisons, two-sided P values <0.05 were considered statistically significant for all comparisons. Analyses were conducted using SPSS version 20.0 (IBM corp, Chicago, Illinois, USA).

Results

Baseline Demographics

The baseline demographics of subjects included in the study are detailed in Table 1. Of the 11170 participants who underwent a colonoscopic biopsy between January 2013 and August 2015, 2862 patients were either excluded because of meeting at least one exclusion criterion or because of missing pathology or endoscopy reports. The remaining 8308 patients were included in the study. Of these, 5260 were male (63.3%) and 3048 (36.7%) female. A total of 10572 colonoscopically resected

polyps were identified; of these, 961 (9.1%) were non-neoplastic, 3757 (35.5%) were serrated adenomas and 5854 (55.3%) colorectal adenomas, including 4272 (40.4%) that were tubular adenomas, 1133 (10.7%) tubulovilla adenomas and 449 (4.2%) that were villous adenomas. The percentage of all histological type polyps was higher in men than women, with 7002 (66.2%) of the polyps identified in men and 3570 (33.8%) in women. Of the total patients enrolled in this study, the highest proportion were 51-60 years of age. Of the 961 non-neoplastic polyps, except for juvenile polyps of which nearly 88% were ⩾10 mm in diameter, more than half of the lymphoid and inflammatory polyps were ⩽5 mm in diameter, while fewer than 10% were ⩾10 mm. A total of 3757 serrated lesions were identified of which 2385 (63.5%) were ⩽ 5mm, 990 (26.4%) were 6-9 mm and 382 (10.2%) were ⩾10mm. Of the 5854 colorectal adenomas, 2020 (34.5%) were ⩽5 mm, 1508 (25.8%) were 6-9 mm, and 2326 (39.7%) at least 10 mm in diameter. Among the 1582 tubulovilla and villous adenomas, 84.6% and 80.6% were at least 10 mm in diameter, 11.2% and 15.8% were 6-9 mm respectively and only less than 5% were ⩽5 mm. Tubular adenomas, on the other hand, showed the opposite trend, 23.5% were at least 10 mm in

diameter and nearly half were ⩽5 mm. Of all polyps, the greatest number were found in the distal colon compared with the proximal colon (63.3% vs 36.7%), especially juvenile polyps, of which more than 90% were in the distal colon. Besides, as shown in Table 2, of the 3588 non-advanced adenomas, 2115 (58.9%) were ⩽5 mm and 1473 (41.1%) 6-9 mm in diameter. Conversely, among the 2266 advanced adenomas, 92.3% were at least 10 mm in diameter, 5.3% were 6-9 mm and only 1.6% were ⩽5 mm. The proportion of patients with non-advanced adenomas decreased, while the percentage with advanced adenomas increasing gradually with increasing age (*P<0.001*). In the proximal colon, the majority of colorectal adenomas were non-advanced adenomas (65.9%), whereas in the distal colon, the percentage of non-advanced and advanced adenomas was similar, P<0.001 for all comparisons.

Gender, Age and Location Distribution of Single vs Multiple Polyps

The difference in gender, age and distribution of location for the single and multiple polyps is detailed in Table 3. Out of 8308 patients, 6843 (82.4%) had single polyps with 1465 (17.6%) having multiple polyps. Among the male patients, 79.2% had single polyps, the remaining 20.8% having multiple polyps, a difference of 3.8-fold, compared with 87.8%

of female patients with single polyps and 12.2% with multiple, a difference of 7.2-fold. Thus, male patients were more likely to develop multiple polyps than females (*P<0.001*).

Patients younger than 40 years old mostly had single polyps, a total of 712 (92.5%) compared with 58 (7.5%) that had multiple polyps. The percentage of patients with single polyps decreased gradually with increasing age, the proportion with multiple polyps increasing gradually. In patients over 71, the proportion with single polyps decreased to 76.2% with 23.8% having multiple polyps (*P<0.001*).

Single polyps were found in 2354 (65.6%) patients with non-advanced adenomas, while 1234 (34.4%) of multiple polyps were found in the same group. Of all patients with advanced adenomas, 1266 (55.9%) had single polyps and 1000 (44.1%) had multiple polyps. There were 1.9-fold as many as patients with single polyps in the non-advanced adenomas group as there were with multiple polyps. While in the advanced adenomas group, there were 1.3-fold as many patients with single polyps than with multiple polyps, as shown in Table 3 (*P<0.001*).

The distribution of single and multiple polyps was as follows: 2893

single polyps in the proximal colon and 3949 in the distal side. A total of 1625 multiple polyps were identified in the proximal colon, while 2105 were distal ($p>0.05$).

Size Distribution of Neoplasia in the Single and Multiple Polyps

As presented in Table 4, and according to the pathological classification, polyps were categorized as either non-neoplastic or neoplastic. Single colorectal adenomas were nearly 2 fold more likely to be 6-9 mm in diameter and nearly 7-fold more likely to be ⩾10 mm than single non colorectal adenomas: odds ratio (OR): 1.93; 95% confidence interval (CI): 1.72-2.17 for 6-9 mm; OR: 6.79; 95% CI: 5.82-7.91 for ⩾10 mm. Multiple colorectal adenomas were 2-fold more likely to be 6-9 mm and 8-fold more likely to be ⩾10 mm than multiple non neoplastic polyps: OR: 2.20; 95% CI: 1.87-2.58 for 6-9 mm; OR: 8.18; 95% CI: 6.69-10.0 for ⩾10 mm.

Size Distribution of Advanced Neoplasia in the Single and Multiple Polyps

Analyses limited to non-advanced and advanced adenomas exhibited even greater differences. Single advanced adenomas were more than

4-fold more likely to be 6-9 mm and 2174-fold more likely to be ⩾10 mm than non-advanced adenomas: OR: 4.29; 95% CI: 2.79-6.58 for 6-9 mm; OR: 2173.87; 95% CI: 1278.44-3696.43 for ⩾10 mm. Multiple advanced adenomas were 4.6-fold more likely to be 6-9 mm and 1865-fold more likely to be ⩾10 mm than non-advanced adenomas: OR: 4.62; 95% CI: 2.50-8.56 for 6-9 mm; OR: 1864.66; 95% CI: 946.83-3672.21 for ⩾10 mm (Table 5).

Among single non-advanced adenomas, 1465 (62.2%) were ⩽5mm in diameter, 889 (37.8%) 6-9mm, there were nearly twice as many diminutive adenomas as small adenomas. While for multiple polyps of non-advanced adenomas, the proportion of diminutive and small adenomas was similar. Compared with single non-advanced adenomas, multiple adenomas tend to be in larger size (*P<0.000*). However, no such difference was observed in the advanced adenomas group (Table 6).

Discussion

The present study demonstrated that adenomas in older individuals was an important predictor of advanced adenomas. Similar results were also

found in the multiple polyps group. With increasing age, the proportion of patients with multiple polyps increased gradually. In the non-advanced adenomas group, patients with small adenomas were more likely to have multiple adenomas compared with patients with diminutive adenomas. More importantly, advanced adenomas were disproportionally more likely to arise from multiple adenomas compared with non-advanced adenomas. In this study, we showed that compared to non-advanced adenomas, advanced adenomas are more common in the distal colon and biopsy of these lesions are recommended. Polyp multiplicity is among the most important predictor both in the US and European CRC screening guidelines that determines when to repeat surveillance colonoscopy. By conducting univariate and multivariate analyses, a retrospective study from Korea demonstrated that the number of adenomas was an independent risk factor of high-risk polyp recurrence.[17] Early study findings demonstrated that the number of advanced adenomas was directly related to the rate of metachronous CRC.[15] In the present study, the risk of advanced adenomas was found to increase progressively with the number of adenomas. This result was confirmed by another study, which suggested that patients with 5 or

more adenomas had a 24% of risk of developing advanced adenomas, nearly 2.7-fold higher than patients with one adenoma.[16] Colorectal advanced adenoma is the most frequent precancerous lesion. Early study findings demonstrated that the number of advanced adenomas was directly related to the rate of metachronous CRC.[15] We have demonstrated a close correlation between neoplastic pathological type and multiple polyps. Patients with multiple adenomas had a high risk of developing CRC.

In addition to the results described above, for the first time an association was found between increased rate of polyp multiplicity, male gender and older age. Multiple polyps were found to be more common in men than in women in the present study. More than 20% of male patients presented multiple instances of polyps, compared with only 10% of women. Population demographics, such as gender, being a risk factor for colon cancer have been previously studied in a number of Western countries.[18,19] Bashar *et al.* used univariate analysis to demonstrate that the prevalence of advanced adenomas was higher in men than in women, suggesting that being male was associated with increased odds of dysplasia. Such findings were confirmed in another study by Martinez *et*

al., who concluded that being male was a moderate risk factor for advanced adenomas.[20] In addition, a study from Japan also revealed that colorectal neoplasms were in general more likely to develop in males.[21] Despite big data and clinical research suggesting that being male is an independent risk factor for CRC, the correlation between the male gender and polyp multiplicity is reported here for the first time.

Older age has been found to be associated with an increased risk of advanced adenomas in previous studies. In this study, we observed the same result. More importantly, we report for the first time that the proportion of multiple polyps increases with patient age, while the percentage of patients presenting single instances decreases. A scientific team from Oakland estimated that the increase in number with age was similar for both men and women, the prevalence rising across all 5-year age categories, reaching a peak at 70-74 years of age. The Chinese consensus of colorectal tumors on prevention and treatment in 2011 reported that the highest incidence of colorectal tumors occurred over the age range 75–80 years.[22] Our findings not only support the current Chinese consensus, but also suggest that colonoscopists should focus on elderly patients with multiple polyps, who may be at risk of colorectal

cancer.

Another interesting finding in this study was the relationship between the size and number of adenomas. We demonstrated that increasing size was a risk factor for both single and multiple colorectal adenomas compared with those that were non-neoplastic. There was a strong correlation between the number and size of adenomas observed in this study for non-advanced adenomas. Multiple non-advanced adenomas were more likely to be larger. However, there was no such correlation between the number and size of advanced adenomas. The USMSTF guidelines recommend 3-year intervals for colorectal cancer surveillance in patients with a history of 3-10 tubular adenomas of any size. This is aimed at minimizing missed lesions or interval cancers, while maintaining the cost-effectiveness and patient adherence to colonoscopy screening. However, the present study suggests that in addition to the number of adenomas, the size of multiple non-advanced adenomas should also be considered in the colonoscopy screening guidelines. The VA study also questioned whether patients who had histories of 3–5 diminutive colorectal adenomas truly had an increased risk of advanced neoplasia compared with patients who had fewer but larger adenomas

during surveillance.[24] The authors found a strong association between baseline screening colonoscopy and rate of serious incident lesions, patients with 1 or 2 non-advanced neoplasia ⩽10 mm representing a low-risk. Although the recommended surveillance interval for one or more tubular adenomas ⩾10 mm is 3 years, the difference in incidence rate in single and multiple non-advanced adenomas suggests that different surveillance and screening interval strategies should be implemented based on the number of polyps identified by colonoscopies.

Conventionally, it is believed that the malignant potential of adenomas correlates with size and location. In the present study, large size was strongly associated with the development of advanced adenomas. In addition, a greater number of adenomas was found in the distal rather than the proximal colon, especially in advanced adenomas. This tendency was observed in patients with either single or multiple polyps.

A shortcoming of this study is that we did not sub-categorize multiple adenomas based on numbers, or investigate the correlation between number and size in these sub-groups. Secondly, the retrospective design of the study in a single-referral center makes it prone to possible

confounders, thus it may have limited application in other regions. Thirdly, the sample size was relatively small. Therefore, a large, multicenter, prospective study will be necessary in the future to confirm the risk factors for multiple polyps.

In conclusion, particular features of colorectal polyps such as large size, advanced neoplastic type in addition to patient demographics such as being male and middle aged are among the associated risk factors of multiple polyps and thus should be incorporated into future guidelines for colorectal cancer surveillance in China.

Acknowledgments

We thank all the doctors and nurses who helped to manage the patients who underwent clinical tests in our department during the months of study.

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Table 1. Baseline characteristics of patients and polyps

Characteristics	All patients (n=8308)	Non-neoplastic polyps (n=961)			Colorectal adenomas (n=5854)		
		Lymphoid polyps (n=243)	Inflammatory polyps (n=676)	Juvenile polyps (n=42)	tubular (n=4272)	tubulovilla[27] (n=1133)	villous (n=449)
Gender							
Male, n (%)	5260 (63.3)	148 (60.9)	473 (70.0)	28 (66.7)	2755 (64.5)	794 (70.1)	298 (66.4)
Female, n (%)	3048 (36.7)	95 (39.1)	203 (30.0)	14 (33.3)	1517 (35.6)	339 (29.9)	151 (33.6)
Age, n (%)							
⩽40	770 (9.3)	47 (19.4)	97 (14. 4)	15 (34.8)	340 (8.0)	48 (4.2)	21 (4.7)
41-50	1810 (21.8)	52 (21.6)	179 (26.5)	15 (34.8)	863 (20.2)	183 (16.2)	80 (17.8)
51-60	2806 (33.8)	77 (31.7)	234 (34.6)	9 (21.7)	1396 (32.7)	383 (33.8)	142 (31.6)
61-70	2127 (25.6)	56 (23.0)	128 (18.9)	3 (8.7)	1201 (28.1)	359 (31.7)	119 (26.5)
⩾71	795 (9.6)	11 (4.3)	38 (38)	0 (0)	472 (11.0)	160 (14.1)	87 (19.4)
Size, n (%)							
⩽5mm		180 (74.1)	495 (73.2)	1 (2.4)	1956 (45.8)	48 (4.2)	16 (3.6)
6-9mm		44 (18.0)	133 (19.7)	4 (9.5)	1310 (30.7)	127 (11.2)	71 (15.8)

⩾10mm		19 (7.9)	48 (7.1)	37 (88.1)	1006 (23.5)	958 (84.6)	362 (80.6)
Location, n(%)							
Proximal colon	3876(36.7)	96 (39.6)	232 (34.3)	4 (8.7)	1840 (43.1)	388 (34.2)	151 (33.6)
Distal colon	6696(63.3)	147 (60.4)	444 (65.7)	38 (91.3)	2432 (56.9)	745 (65.8)	298 (66.4)

Table 2. Patients Gender, Age, and Adenomas Features

	Colorectal polyps (n=5854)		
	Non-advanced Adenomas(NA) (3588)	Advanced Adenomas(AA) (2266)	P value
Gender			
Male, n (%)	2342 (60.9)	1505 (39.1)	0.482

Female, n (%)	1246 (62.1)	761 (37.9)	
Age, n (%)			
<=40	282 (76.2)	88 (23.8)	<0.001
41-50	757 (70.7)	313 (29.3)	
51-60	1158 (59.7)	783 (40.3)	
61-70	1015 (57.2)	759 (42.8)	
>=71	376 (53.8)	323 (46.2)	
Location, n (%)			
Proximal colon	1677(65.9)	866(34.1)	P<0.001
Distal colon	1908(57.6)	1403(42.4)	

Table 3.

Demographic Characteristics, Polyp Pathology and Location of Single and Multiple Polyps

	Single	multiple	P value
Gender			
Male	4168	1092	P<0.001
n (%)	(79.2)	(20.8)	
Female	2675	373	
n (%)	(87.8)	（12.2)	
Total			
	6843	1465	
Age, n (%)			
⩽40	712	58	p<0.001
	(92.45)	(7.5)	
41-50	1580	230	
	(87.3)	(12.7)	
51-60	2284	522	
	(81.4)	(18.6)	
61-70	1661	466	
	(78.1)	(21.9)	
⩾71	606	189	
	(76.2)	(23.8)	
Colorectal adenomas			

Non-advanced adenomas n (%)	2354 (65.6)	1234 (34.4)	P<0.001
Advanced adenomas n (%)	1266 (55.9)	1000 (44.1)	
Proximal colon	2893 (64.0)	1625 (36.06)	P>0.05
Distal colon	3949 (65.2)	2105 (34.8)	

Table 4. Odds Ratios of Neoplastic Pathology Stratified by Polyp Size

	Non- neoplastic polyps	Colorectal adenomas	OR (95% CI)	adjusted OR (95% CI)

Single				
⩽5mm	2111	1495	reference	reference
6-9mm	708	967	1.93(1.72-2.17)	1.87 (1.66-2.10)
⩾10mm	241	1158	6.79 (5.82-7.91)	6.75 (5.77-7.88)
Multiple				
⩽5mm	860	663	reference	reference
6-9mm	377	638	2.20(1.87-2.58)	2.08 (1.76-2.45)
⩾10mm	148	933	8.18(6.69-10.0)	7.87 (6.43-9.64)

Table 5. Odds Ratios of Advanced Pathology Stratified by Polyp Size.

	Non-advanced adenomas	Advanced adenomas	OR (95% CI)	Adjusted OR (95% CI)
Single				
⩽5mm	1465	30	reference	reference
6-9mm	889	78	4.29 (2.79-6.58)	4.18 (2.71-6.42)
⩾10mm	0	1158	2173.87 (1278.44-3696.43)	2212.16 (1289.28-3795.66)
Multiple				
⩽5mm	650	13	reference	Reference
6-9mm	584	54	4.62 (2.50-8.56)	4.52 (2.43-8.39)
⩾10mm	0	933	1864.66 (946.83-3672.21)	1976.94 (992.17-3939.15)

Table 6. Difference in Size Distribution Between Single and Multiple Adenomas

	Single	Multiple	P value

	n=2380		n=1259		
	n	%	n	%	
≤5mm	1465	62.2	650	52.7	
6-9mm	889	37.8	584	47.3	†P=0.000

†≤5mm vs 6-9mm P=0.000

Advanced adenomas

	Single n=1240		Multiple n=975		P value
	n	%	n	%	
≤5mm	30	2.4	13	1.3	
6-9mm	78	6.2	54	5.4	†P=0.102
≥10mm	1158	91.5	933	93.3	‡p=0.061

†≤5mm vs 6-9mm P=0.212

‡≤5mm vs ≥10mm p=0.061